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Review article

Clinical and basic research on steroid-induced osteonecrosis of the femoral head in Japan☆

Toshikazu Kubo*, Keiichiro Ueshima, Masazumi Saito, Masashi Ishida, Yuji Arai, Hiroyoshi Fujiwara

Department of Orthopaedics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

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ABSTRACT

Background: Steroid (glucocorticoid)-induced osteonecrosis of the femoral head (ONFH) in young adults has been a challenging disorder due to frequent incidence of collapse of the femoral head and resulting dysfunction of the hip joint and impairing quality of life. In Japan, the working group on ONFH in the Specific Disease Investigation Committee under auspices of the Japanese Ministry of Health, Labor and Welfare was founded in 1975, clinical and related basic research on ONFH have been continued for more than 40 years.

Epidemiology and clinical course: A national epidemiologic survey in 2004 estimated that 2200 new patients per year would be diagnosed with ONFH in Japan. ONFH was associated with steroid intake (51%), heavy alcohol intake (31%), both (3%), and neither (15%). The male-to-female ratio was 5:4, and the peak decades of age at definitive diagnosis were the 40s in male patients and the 30s in females. MRI studies revealed that ONFH would have occurred in early phase after start of steroid administration and no expansion of necrotic lesion within the femoral head in spite of continued steroid use. To standardize ONFH diagnosis and treatment strategy, the Committee established validated diagnostic criteria, a radiological staging system, and type categorization.

Treatment options: Most symptomatic patients with collapse of the femoral head require various surgical procedures. Joint preserving surgery, such as transtrochanteric rotational osteotomy and curved varus osteotomy, should be the treatment choice for young patients with healthy areas without severe collapse of the femoral head.

Clinical and related basic research: Clinical and basic research has been performed to determine the pathogenesis of steroid-induced ONFH. Low hepatic CYP3A activity has been reported to significantly contribute to the risk of steroid-induced ONFH. Several gene polymorphisms related to steroid metabolism were shown to be associated with the occurrence of ONFH.

Contents

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* Corresponding author. Tel.: +81 75 251 5549; fax: +81 75 251 5841.
E-mail address: tkubo@koto.kpu-m.ac.jp (T. Kubo).

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1. Introduction

Steroid (glucocorticoid)-induced osteonecrosis of the femoral head (ONFH) in young adults has been a challenging disorder due to frequent incidence of collapse of the femoral head and resulting dysfunction of the hip joint and impairing quality of life. The causes of ONFH have not been clarified; however, studies have suggested that this disease is associated with the administration of steroids in patients with connective tissue diseases and organ transplant recipients, as well as with heavy alcohol intake [1,2]. In particular, steroid-induced ONFH, which may have iatrogenic aspects, occurs frequently in adolescents and middle-aged patients. Therefore, it is necessary to standardize diagnosis and treatment and to develop highly reliable methods of prevention.

In 1975, the working group on ONFH in the Specific Disease Investigation Committee (the Committee) was established under the auspices of the Japanese Ministry of Health, Labor and Welfare to conduct clinical and related basic research studies on ONFH. Research has been ongoing for more than 40 years. The Committee has continuously published the latest research results on aspects of ONFH, including epidemiological surveys [2–4], diagnosis and treatment [5,6], clinical [7–9] and basic research [10,11] and is making a contribution on a global level.

This article discusses the epidemiology, pathology and treatment of steroid-induced ONFH, based on the results of research conducted by the Committee.

2. Epidemiology

A national epidemiologic survey in 2004 estimated that approximately 11,400 patients in Japan were treated for ONFH annually, and that 2200 patients per year were newly diagnosed with this disease. The male-to-female ratio was 5:4, and the peak decades of age at definitive diagnosis were the 40s in male patients and the 30s in females (Fig. 1). ONFH was estimated to be associated with steroids in 51% of patients, with heavy alcohol intake in 31%, with both in 3%, and with neither in 15%. ONFH was found to be steroid-induced in 34% of male patients and in 76% of females. The underlying diseases requiring steroid administration included systemic lupus erythematosus (SLE) in 31.2%, nephritic syndrome in 6.3%, polymyositis/dermatomyositis in 4.9%, asthma in 4.5%, thrombocytopenic purpura in 4.4%, and other connective tissue diseases in the remainder [3]. A multi-institutional case–control study found that the risk of ONFH was 20-fold higher in patients with than without a history of oral steroid administration [4].

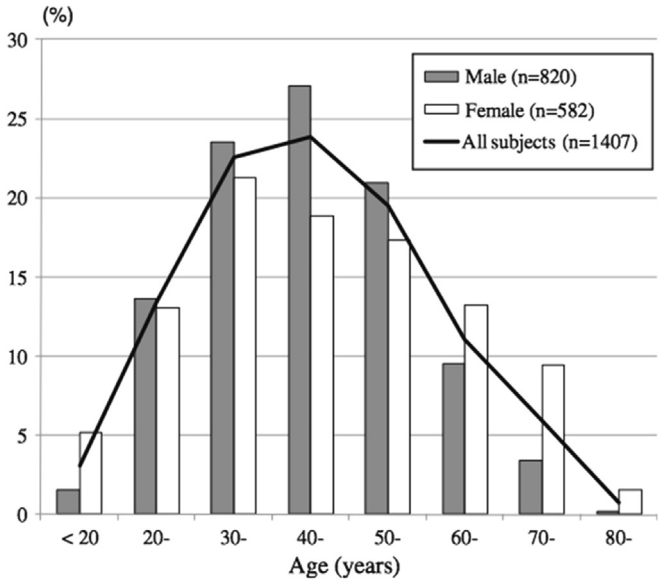

Fig. 1. Age distribution (in years) of subjects at the time of diagnosis of ONFH. Analysis was based on subjects of known age at the time of diagnosis.
Source: [3].

Case–control studies were performed in Japanese SLE patients [12] and kidney transplant recipients [13] to determine the association between steroid dose and ONFH. These studies, which assessed the association between occurrence of ONFH and accumulated steroid dose in a year, maximum dose and average daily dose, found that average daily steroid dose had the strongest effect on occurrence of ONFH. SLE patients receiving more than 16.6 mg/day prednisolone had a 3.4-fold higher risk of ONFH compared with patients receiving less than 12.3 mg/day [12]. Similarly, kidney transplant recipients receiving more than 20.40 mg/day prednisolone had a 5.0-fold higher risk of ONFH compared with patients receiving less than 14.92 mg/day [13].

The multifocal osteonecrosis associated with steroid administration may occur not only in femoral heads but in humeral heads, knee joints and ankle joints. It was reported that 91% of patients with multifocal osteonecrosis had a history of steroid administration [14]. An MRI screening study of 250 patients with steroid induced ONFH found osteonecrosis in 50% of knees and 24% of humeral heads [15].

3. Clinical course of steroid-induced ONFH

In spite of many extensive studies of ONFH, it has been obscure how ONFH occur after start of steroid use. However, timing of ONFH occurrence after start of steroid use was investigated by time sequential MRI in a cohort of renal transplantation recipients with postoperative steroid use for the purpose of immuno-suppression. With the exception of cases who failed to be MR imaged until 12 month postoperatively, all ONFH lesions were first detected on MRI within 16 week after transplantation [7,16]. Thus, steroid-induced ONFH would occur in early stage of steroid therapy. In considering other MRI study result in traumatic ONFH that advent of the T1 weighted band image on MRI was noted 4 weeks after interruption of blood circulation by the fracture [17], the onset of ONFH caused by ischemic attack in femoral head might assumed to occur 2–12 weeks after start of steroid use.

In those ONFH patients, symptom (hip pain), which would be caused by collapse of the femoral head, started 6 months to 2 years after renal transplantation and the start of steroid use (Fig. 2) [7]. Similar intervals from the start of steroid use to hip symptom (1–4 years) was reported by other authors in a SLE cohort [8].

For ONFH patients requiring continuation of steroid use for the treatment of back ground diseases, there might be concerns for

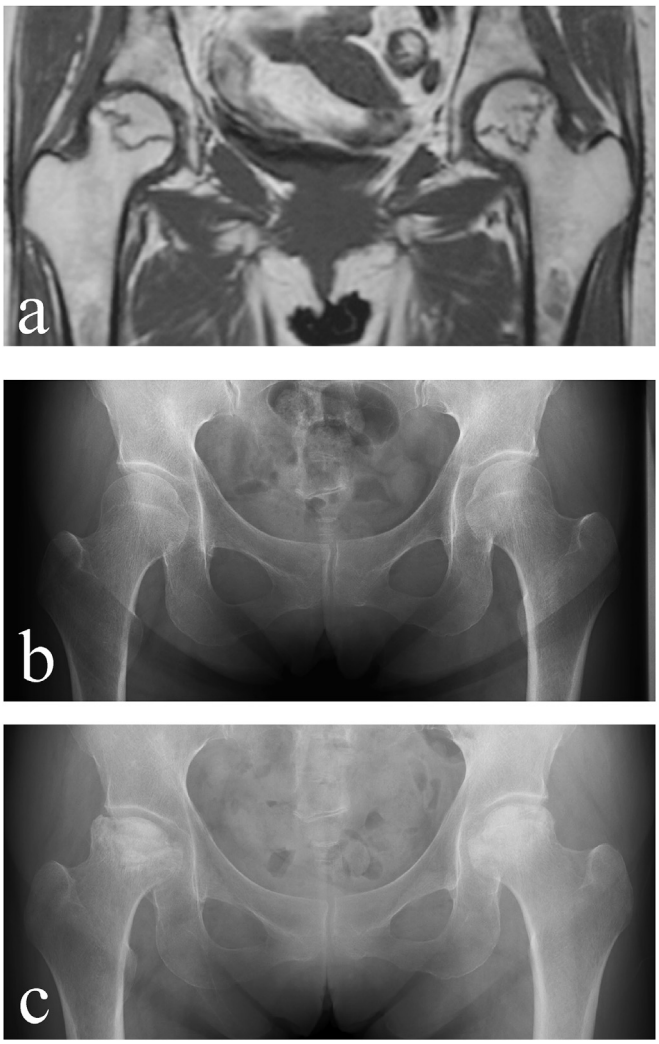

Fig. 2. Progression of ONFH after renal transplantation. a. T1-weighted MRI of hip joints 12 weeks after renal transplantation. T1 low-intensity band patterns were observed in the bilateral femoral head. b. Plain radiograph of hip joints 12 weeks after renal transplantation. No abnormal findings were observed in the femoral head. c. Plain radiograph of hip joints one year after renal transplantation. Demarcation of sclerosis and collapse were observed in the bilateral femoral head.

expansion of the necrotic lesion or additional recurrence of bone necrosis in other sites. The studies to address this concern indicated no expansion of the necrotic lesion with continuous use of steroid [7]. And once the site and size of the necrotic lesion were fixed, additional bone necrosis lesions were extremely rare to appear [18,19]. Sugano et al. reported that shift from unilateral ONFH cases to bilateral cases is very rare (2%) [20].

These observations suggested that the prognosis of the affected hip can be predicted based on the initial position and size of the necrotic area. Moreover, as the rate of recurrence is low even if steroids are continued, there is no need to reduce steroid dosage or discontinue their administration after the occurrence of ONFH, since steroids remain necessary to control the underlying disease.

4. Diagnosis and treatment strategy for ONFH

The Committee devised a tool for diagnosis consisting of 5 characteristic features of typical ONFH on plain radiograph, bone scintigram, MRI and bone biopsy findings (Table 1) [5]. Validity of the diagnostic tool was examined in patients with hip disorders with histology of excised whole femoral head as gold standard. Sensitivity and specificity of the diagnostic tool were calculated to be 91% and 99%, respectively [6].

In order to predict prognosis of ONFH in early stage, Four types (A, B, C1 and C2) were classified based on size and location of necrotic area on A/P X-ray and/or MRI mid-coronal image of the femoral head, i.e. depending on location of subchondral necrotic bone mass in relation to acetabular weight bearing surface line (Fig. 3) [5]. Survivorship of the ONFH hips without femoral head collapse in respective groups was already reported [21]. Poor prognosis was consistently shown in type C (C1 and C2) group. Identification of stage of destructive changes in ONFH also would be important step to find optimal surgical option. And the Committee has presented a grading system (Table 2, Fig. 4), based on the occurrence of the femoral head collapse and osteoarthritic changes [5]. The Committee recommends deciding optimal surgical treatment by considering type and stage of the ONFH as described below.

4.1. Conservative treatment

Natural courses of the early ONFH without collapse were observed in time sequence without any treatment and presented in several reports [21–23]. A systematic review found that types A, B and C hip collapses occur in 9%, 19%, and 59% of ONFH patients, respectively [21]. In addition, cessation of collapse and improvement of symptoms without surgical intervention can occur in patients with type A and B hips once the femoral head has collapse [23,24]. Most of type A hips survived without collapse and progressive symptoms. Therefore, type A and type B hips with no or mild symptom would allow to be observed without treatment. But poor prognosis was predominantly seen in type C group hips. Type C hips and a part of type B hips frequently progress to collapse and would be candidates for surgery despite use of analgesics.

As collapse is the major cause of symptom, prevention of collapse with drugs, if possible, might be a target of conservative treatment. Administration of bisphosphonate was reported to prevent collapse in early stage ONFH in small groups of patients [24]. However, prolonged anti-collapse effect of bisphosphonates was not elucidated yet. Further extensive studies with long-term observation would be warranted.

Table 1
Diagnostic criteria for osteonecrosis.

Collapse of the femoral head without joint space narrowing or acetabular abnormality on X-rays (including crescent sign)
Demarcating sclerosis in the femoral head without joint-space narrowing or acetabular abnormality on X-rays
“Cold in hot” on bone scans
Low intensity band on MR T1-weighted images (band like pattern) within the femoral head
Trabecular and marrow necrosis on histology
Definite diagnosis requires any two positive criteria out of the five.
Bone tumors and dysplasias should be excluded.

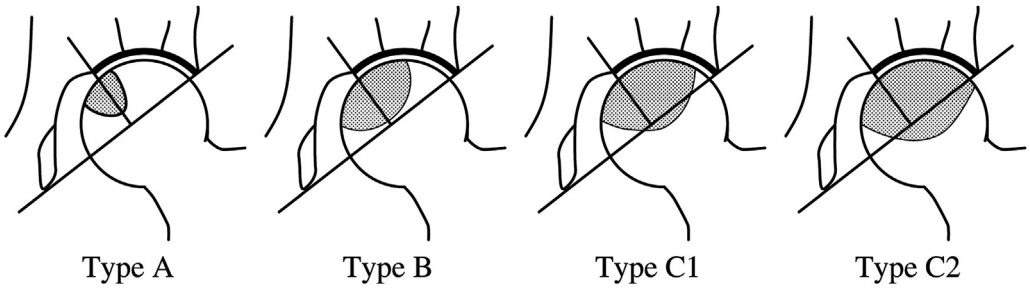

Fig. 3. 2001 revised classification of osteonecrosis. The classification scheme consists of four types (A, B, C1, and C2) and is based on the anteroposterior X-rays or mid-coronal section of the femoral head on T1-weighted MR images. Type A lesions occupy the medial one third or less of the weight-bearing portion. Type B lesions occupy the medial two thirds or less of the weight-bearing portion. Type C1 and type C2 lesions both occupy more than the medial two thirds or less of the weight-bearing portion; type C2 lesions extend laterally to the acetabular edge type, whereas C1 lesions do not. The weight-bearing portion is defined as the area lateral to the mid-vertical line of the line through the acetabular edge and the teardrop bottom.

4.2. Surgical therapy

Surgery is indicated in patients with symptoms that are expected to progress to collapse of the femoral head. Surgical methods to treat ONFH would largely be classified to two categories, joint preserving surgeries and prosthetic replacement surgeries. The joint preserving surgical procedures would include core decompression with or without bone grafting (non-vascularized or vascularized), transtrochanteric osteotomy (transtrochanteric anterior or posterior rotational osteotomy (TRO)) and curved varus osteotomy (CVO). According to multicenter survey by the Committee in 2007, joint preserving surgeries were underwent in 1/4 cases and prosthesis replacing surgeries in 2/3 cases in Japan [25]. The joint preserving surgeries were ordinarily indicated for young or middle-aged patients without collapse (stage 2) or with mild collapse (stage 3A).

Before MRI became common, core decompression (core biopsy) was the most reliable diagnostic modality for ONFH [26]. A recent review article indicated that core decompression provides favorable outcomes only in patients with small necrotic lesions [27]. However, anti-collapse effect of the core decompression in early stage of has been controversy. Since Sugano et al. reported little anti-collapse effect of the core decompression in high collapse risk type C [28], this surgery without bone grafting would rarely be indicated in Japan.

Non-vascularized bone grafting for early-stage ONFH has been reported [29], but this procedure has not been widely adopted. Previously, vascularized bone grafting from iliac crest or fibula after curettage of necrotic bone mass was attempted but clinical results were not always successful due to post-operative progression of collapse, in despite of bone defects at graft harvesting sites and demanding skills of micro-surgery [30,31].

The principle goals of osteotomy for ONFH are to avoid load stimulation on necrotic parts, and to achieve joint congruity by returning the femoral head from the subluxation to the concentric position. Currently, good clinical results have been reported in cases of TRO and CVO in early stages (stage 2 or 3) [32–34]. TRO is aimed at shift of the necrotic bone mass from weight-bearing sub-chondral part and to be replaced with healthy bone with smooth cartilage surface through anterior or posterior rotation of the femoral head and neck around femoral neck axis after inter-trochanteric osteotomy (Fig. 5). TRO is mainly indicated in patients with type C-1 and C-2 hips, in which healthy areas remain in the anterior or posterior part of the weight-bearing area. Decision of anterior or posterior rotation was ordinarily made depending on location of the necrotic bone mass on lateral radiograph. Anterior rotational osteotomy would be recommended when the necrotic bone mass in the femoral head located anterior part under weight-bearing surface to the femoral head. Since the necrotic bone mass shift outside of the weight-bearing surface and healthy mass locating posterior part of the head shift to weight-bearing surface, resulting higher rate of coverage of the femoral weight-bearing surface with healthy bone and cartilage. When the subchondral necrotic mass locates more cranial or posterior part of the femoral head, posterior rotational osteotomy would be recommended due to the concept described above. Success rates in previous reports of TRO were around 80% [32,33]. Preservation of vasculature to the femoral head was reported to essential to obtain good clinical results and great care should be taken intra-operatively to avoid damage to vasculature to femoral head. Based on recent follow-up studies of the post-operative patients of TRO, the ratio of shifted healthy joint surface to acetabular weight-bearing on A/P radiograph appeared to be a critical factor for long term hip function, and the ratio more than 34% would be necessary to keep good hip function [35].

The aim of CVO was similar to the rotational osteotomies. By CVO, healthy bone and cartilage in lateral part of the head was shifted to weight-bearing part of the head (Fig. 6). But the shift distance of the healthy bone mass was limited compared with TRO. And this osteotomy would be indicated to symptomatic type B and/or type C-1. In comparison with TRO, advantages of this osteotomy

Table 2
Staging system for ONFH.

Stage 1. There are no specific findings of osteonecrosis on X-ray images. However, specific findings are observed on MRI, bone scintigram, or histology.
Stage 2. Demarcating sclerosis in seen without collapse of the femoral head.
Stage 3. Collapse of the femoral head, including crescent sign, is seen without joint-space narrowing. Mild osteophyte formation of the femoral head or acetabulum may be seen.
Stage 3A. Collapse of the femoral head is less than 3 mm
Stage 3B. Collapse of the femoral head is 3 mm or grater
Stage 4. Osteoarthritic changes are seen
Staging should be based on both anteroposterior and lateral X-ray views of the femoral head. The lateral view of the femoral head should be taken in the anteroposterior direction while the patient is positioned supine with the hip in 90° of flexion, 45° of abduction, and neutral rotation, according to the Sugioka method.

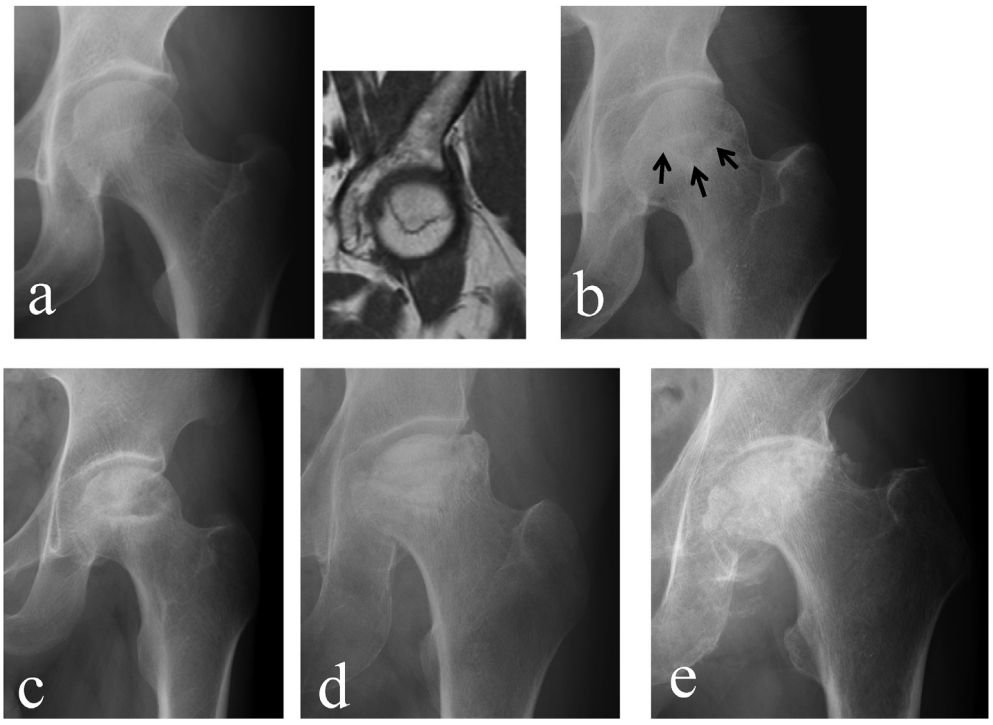

Fig. 4. Radiographic findings of the staging system for ONFH. a. Stage 1. No specific findings on plain radiographs, but a low-intensity band pattern was observed on T1-weighted MRI. b. Stage 2. Demarcation of sclerosis observed in the femoral head (arrows). c. Stage 3A. d. Stage 3B. e. Stage 4.

were with little risk for damage to vasculature to the femoral head and not requiring highly demanding surgical skill [34].

Regarding prosthetic replacement surgery, bipolar hip arthroplasty (BHA) had been one of routine options for ONFH patient until recent years due to simple surgical procedures and preserved acetabular bony structure. But later follow-up studies of those patients indicated high rate of progressive central migration of prosthesis, stem loosening and revision surgery [36,37]. Previously, clinical outcome of total hip arthroplasty (THA) in ONFH had been definitely inferior to that of osteoarthritis (OA) due to high rate of loosening, dislocation and subsequent limited survivorship due to high demands to physical activity [38]. But modern THA is accepted for major treatment of choice for ONFH patients despite of younger mean age of those patients compared with that of OA patients. This might resulted from significant improvement of prosthesis (biomaterials, design, and porous surface) and modern surgical technique. And survivorship of the THA in ONFH patients was significantly improved and equivalent to that in OA patients [39]. One of the remaining concerns for THA in ONFH patients is high rate of post-operative dislocation compared with that in OA patients [40].

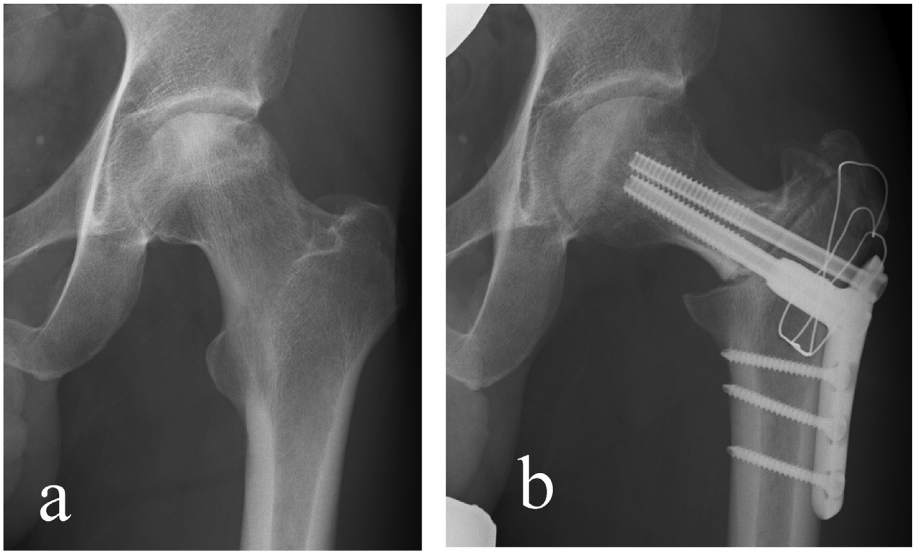

Fig. 5. Transtrochanteric anterior rotational osteotomy of the femoral head. a. Plain radiograph of hip joint before surgery, showing Type C-2 ONFH. b. Plain radiograph after surgery. The necrotic area was shifted medially.

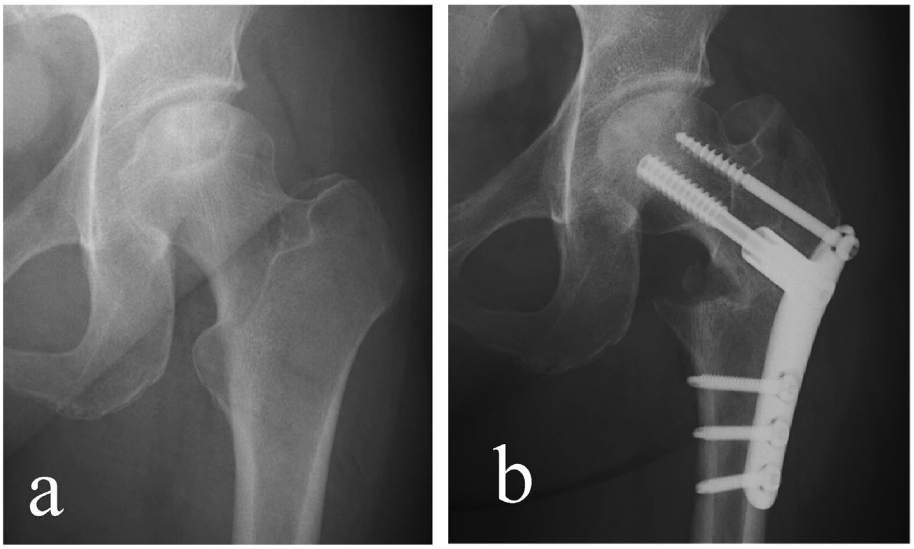

Fig. 6. Curved intertrochanteric varus osteotomy. a. Plain radiograph of hip joint before surgery, showing Type C-1 ONFH. b. Plain radiograph after surgery. The necrotic area was shifted medially.

Use of large ball, double bearing prosthesis and/or anterior approach would be recommended to avoid the dislocation.

5. Clinical and related basic research on ONFH

In order to elucidate patho-mechanism of steroid-induced ONFH, lots of experimental projects were designed and performed by the Committee members. The pathogenesis of steroid-induced ONFH has been reported to involve oxidative stress [41], disorders of the vascular endothelium [42], blood coagulation disorders, abnormal lipid metabolism [43], fat embolism [44] and apoptosis [45]. Recent topic on mechanism of steroid was oxidative stress, which might damage vascular endothelial cells of arteries or arterioles to incite ischemic attack within femoral head. Thus excessive oxidative stress potentially causes ischemic bone necrosis [11,41]. Therefore, amelioration of the oxidative stress with anti-oxidative drugs, like vitamin E, might be effective to prevent bone necrosis by concomitant administration with steroid. Administration of vitamin E has been found to prevent steroid-induced osteonecrosis in animal models [46]. This hypothesis should be substantiated in following studies.

Regarding individual difference in susceptibility to steroid induced ONFH, Kaneshiro et al. evaluated steroid metabolizing enzyme hepatic cytochrome P450 (CYP) 3A enzyme activity by measuring midazoram clearance and concluded that CYP3A activity in steroid-induced ONFH patient was consistently lower than standard level of normal population [9]. And he speculated that patients with low steroid metabolizing capacity would be exposed to higher level of steroid for prolonged period time, and resulting toxic effects, e.g., high level of oxidative stress. By regulating CYP3A capacity with agents inducing or suppressing the CYP3A enzymatic activity, association of CYP3A activity with vulnerability to steroid induced bone necrosis was shown in a rabbit model [10].

Some renal transplant recipients develop steroid-induced ONFH, while others receiving the same steroid administration protocol do not [47]. These inter-individual differences may be associated with genetic polymorphisms. Single nucleotide polymorphisms (SNPs) of P-glycoprotein (P-gp), a transport protein that exports drugs such as steroids from inside to outside the cell [48], and of glucocorticoid receptors [49] have been found to affect the occurrence of ONFH.

6. Summary

This report provided an overview of the clinical and related basic research on ONFH conducted by the Committee. The number of ONFH patients and the risks of steroid administration were demonstrated by the national epidemiologic survey. MRI showed that early stage, asymptomatic ONFH occurred soon after starting steroid administration, with no expansion of necrotic lesions within the femoral head despite continued steroid use. To standardize ONFH diagnosis and treatment, the Committee established diagnostic criteria, a radiological staging system, and type categorization. Categorizing disease stage and type following a diagnosis of ONFH enables selection of the appropriate treatment. Clinical studies showed that low hepatic CYP3A activity and several gene polymorphisms were significantly associated with the risk of steroid-induced ONFH. Intensive basic research has been performed to clarify the pathogenesis of ONFH.

Conflict of interest

The authors declare that they have no conflict of interest.

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